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ORIGINAL ARTICLES

SEVERE ANEMIA CONNECTED WITH GASTRO-INTESTINAL DISEASES.[1]

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Although not aware of the frequency of pernicious anemia in the United States, I believe that in Europe it is becoming more and more frequent. When studying the different kinds and manifestations of intestinal dyspepsia, I met with more or less severe anemia, and will state the relationship existing between these two morbid conditions.

Combe, Addison, and Biermer first described certain cases of anemia, marked by their intensity and fatal issue, as idiopathic or pernicious anemia. They based their reasons for separating this particular anemia from the common type not only on the serious character of its clinical symptoms—high degree of blood changes, fever, extravasations of blood, digestive troubles, etc.—but also on the absence of any organic lesion which could be regarded as the origin of the disease and the lack of any conceivable etiology. This manner of defining a new clinical disease chiefly by negative symptoms, though corresponding to the state of science at that time, could not be satisfactory. Thus the discussion about the nature and the conception of the disease began and has continued, producing numerous facts and theories, but not at all solving the problem.

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[1] Delivered before the Harvey Society, October 18, 1913.

One of these facts is the discovery, made by Russian and Danish authors, especially by Rosenquist, Schaumann, and Talquist, that infection with bothriocephalus is able to cause a form of progressive anemia which by no means can be separated from Biemer's pernicious type. With that the idiopathic or primary character of the disease became doubtful. But though there were found subsequently other causes of the disease, as syphilis (Fr. Müller), pregnancy (Gusserow), etc., the remaining number of unexplained cases was still large.

In interpreting these cases from 1900 to the present time, two different theories are mostly discussed: according to one of them, inaugurated by Paul Ehrlich, the characteristic sign of the disease is the megaloblastic degeneration of the blood-forming structures; the other, advocated by W. Hunter, starts from the hemolytic nature of the disease and supposes its origin to be found in a more or less specific affection of the gastro-intestinal tube.

Ehrlich's hematological studies, by means of differential staining, led him to the conclusion that a distinct type of bone-marrow change, which causes the appearance of large and intensely colored, partially nucleated red corpuscles—megalocytes and megaloblasts—cell forms which under normal conditions appear only in embryonic life, is not only the essential symptom but even the cause of pernicious anemia. He and his followers (Lazarus, Engel, Naegeli, and other hematologists) speak of pernicious anemia only if this sign and some other blood changes, as increased color-index, poikilocytosis, diminished number of leukocytes, with comparative increase of lymphocytes, are evident.

There can be no doubt that by accepting Ehrlich's theory the conception of the disease, given by Addison and Biemer, is changed to some extent, for clinical observation shows that megaloblastic degeneration may be present in some cases of common (secondary) anemia and absent in others belonging to the idiopathic group. The megaloblastic type of blood formation, though a characteristic symptom of the disease, as is the pigmentation of internal organs and the tendency to hemorrhages does in no way explain the etiology. If pigmentation is the cause of hemolysis, the changes in blood formation must be taken as reactions of the bone marrow to the unknown cause of hemolysis (Naegeli).

Hunter was the first to perceive the hemolytic nature of pernicious anemia. After him this form is distinguished from all other forms by the excessive presence of iron in the liver, due to the more or less continuous destruction of red corpuscles within the portal circulation. Though he could not prove the presence of the hemolytic process itself nor produce the hemolytic substance from the organs, he tried to confirm his theory by indirect arguments, especially by demonstrating the constant presence of glossitic lesions, which he supposed to be caused by streptococcic infection, and by finding an increased amount of aromatic sulphates and other products of intestinal putrefaction in the urine of his patients.

Hunter's observations, at first neglected in consequence of the attention generally bestowed upon Ehrlich's studies, have found valuable support through E. Grawitz and other clinicians. But his theory could not be accepted before the supposed hemolytic principle was brought into evidence. This was done in 1907 by Tallquist in bothriocephalus anemia, the best studied form of enterogenous anemia. Only a small percentage of patients harboring tape-worm suffer from anemia. Tallquist estimates the occurrence to be less than 1 per cent. Though this disease in its severer forms shows all symptoms of pernicious anemia, the blood is by no means always megalocytic or even megaloblastic. Sometimes in the beginning there are found glossitic lesions analogous to those described by Hunter. Nitrogen metabolism is periodically altered so that increased decomposition of albuminates must be accepted (Rosenquist). The substance which causes hemolysis is produced in the tape-worm itself, not in the healthy one, but in degenerated parts of it by an autolytic process. It is a cholesterin ester of oleic acid, which in small quantity also may be obtained from different normal organs. If the bothriocephalus is removed by efficient treatment the patients may entirely recover, but in some cases there still remains an increased tendency to the recurrence of anemia (Schaumann).

Bothriocephalus is not the only worm the presence of which gives rise to anemia, as the hook-worm, which sucks blood from the mucous membrane, thus leads to successive anemia. But as it produces no toxin, the megaloblastic blood degeneration is missing. On the other hand, there have been described some undoubted observations of the pernicious form connected with the common tape-worm (Tenia saginata) and with trichocephalus, round-worm, and certain protozoic infections. Even in tropical sprue an anemic condition of severe character is sometimes seen, although exact investigations of blood changes are not yet published.

Regarding the hemolytic nature of bothriocephalus anemia, it is natural to suppose similar conditions in other forms of anemia connected with gastro-intestinal disorders. Besides the large class of unexplained idiopathic anemias, there are two more morbid states which from this point of view excite our interest—namely, the coincidence of a small non-ulcerated stomach cancer, with progressive anemia of the megaloblastic type, and the development of the same pernicious form in the course of cicatricial stenosis of the small intestine.

As regards the first condition, the fact is well known that the so-called cancer anemia appears especially in cancers of the gastro-intestinal tract. Though the blood generally does not show the characteristic signs of toxic bone-marrow reaction, hemolytic substances comparable to those of the bothriocephalus body have been separated from cancerous tissue by Kullmann, Tallquist, and others. They may be, but seldom are strong enough to overcome the regenerative power of the blood-forming organs. In the cases referred to, the postmortem examination did not exhibit any other cause of the anemia, as, for instance, inflammation of the mucous membrane, cancerous degeneration of the bone marrow, etc. v. Noorden, Israel, Scott, Bloch, Lazarus, Nauer have observed such cases, and I can add two of my own. Shall we regard this coincidence as chance? Are there two different diseases coexistent? I think it is difficult to deny entirely any connection between them.

The second condition, cicatrised tuberculous stenosis of the small intestine, accompanied with pernicious anemia, was first described by Faber and Borchgrevink. Most of the cases hitherto known showed no fresh ulcerations nor any notable inflammation. In my own two observations even microscopic investigation demonstrated only the same state of insignificant lymphocytic infiltration of the mucous membrane, as in other cases of pernicious anemia. Neither the preëxisting tuberculous ulceration nor the scars, but only the irrigation of the intestinal walls following the chronic retention of the contents, can be regarded as the etiology.

The group of unexplained cases of pernicious anemia in relation to gastro-intestinal troubles now claims our attention. Biemer has described certain digestive disturbances, as anorexia, gastric discomfort, weak digestion, and periodic diarrhea, as the chief symptoms of the disease called after him; but he regarded them as consequences of the anemia, as did succeeding observers except Hunter. Hunter says: "A history of antecedent gastric or intestinal disturbances was found in each of twenty-five cases. In no case were these of sufficient character or intensity to account for the supervention of such an intense degree of anemia. The various disturbances connected with this tract have an important sigficance, not as a cause of the disease, but as symptoms of the gastric and intestinal infective lesions associated with the disease." In other words, anatomical lesions, especially the infective glossitic changes, are the chief factors; the digestive troubles are only the mild manifestations of these lesions.

According to the more physiological point of view of modern clinical investigation we will first consider these functional disorders. The fact of the constant absence of hydrochloric acid in the gastric contents of all patients suffering from pernicious anemia was somewhat neglected until Martius found out that we had to deal not only with a defect of hydrochloric acid, but of the whole gastric digestion, *i. e.*, with achylia gastrica. Even this fact did not attract much attention, for by the more common use of the stomach-tube it soon became evident that many persons who have no gastric juice do not suffer from any digestive trouble, and that this condition does not depend necessarily on atrophy of the gastric glands. But the conception has considerably changed. Since Oppler and Einhorn first described chronic diarrheas following gastric achylia the different forms of gastrogenous intestinal dyspepsia have become an object of clinical interest, the consequences of which cannot yet be fully estimated. Faber, who analyzed 207 cases of achylia, found in 22, or 11 per cent., marked signs of pernicious anemia, and in 22 others a hemoglobin o less than 50 per cent. While the anemia in these latter cases only showed the character of a serious chlorosis, in the others all the blood changes of the pernicious form were present; increased color-index, poikilocytosis, leukopenia, and megaloblastic degeneration of the red corpuscles. Furthermore, Faber observed a number of patients suffering from severe anemia, whose achylia had already existed and had been proved many years before they fell sick with anemia. This fact led him to the conclusion that pernicious anemia is not, as generally supposed, the cause of gastric achylia, but, on the contrary, the result of it.

Coming now to the intestines, it was Grawitz who, following Hunter's suggestion, attached most weight to enterotoxic products, which he supposed to result from insufficient or faulty denaturation of the albuminates. Unfortunately, he also was unable to produce any argument which could confirm his theory. I therefore first undertook to study the frequency and kind of the intestinal troubles, mentioned by most authors as a symptom of the disease, but not yet analyzed by anyone.

Among my patients suffering from idiopathic pernicious anemia there were sixteen, the third part of all observed, who showed more or less marked signs of intestinal disorders. They mostly had periodic diarrhea, or diarrhea alternating with constipation. Generally the diarrhea was of an insignificant degree, and was not accompanied with colicky pains.

When examined by means of my test-diet or similar food, the feces were of a pulpy consistency, and had an offensive odor, which sometimes was distinctly sour. Corresponding to that the reaction was either markedly alkaline or acid, the normal test-diet stool being nearly neutral. When ground up with water to a fluid consistence, often small flakes of mucus could be seen, whereas larger particles were constantly missing. A few times the whole mass showed a mucous condition, though no flakes could be isolated. Chemical tests showed that this condition was caused by the presence of a large quantity of nucleoproteid, a product of the intestinal epithelium, which under normal conditions appears only in small quantity.

As to the remains of food, connective tissue was often found, due to the lack of gastric juice. Macroscopic remains of muscular tissue seldom could be seen, but often increased quantities of microscopic muscle fragments. Starch granules colored blue with iodine and numerous needles of fatty acid and soaps were easily defined by the microscope. The fermentation test at times was positive.

Interpreting these facts we have to deal with a kind of intestinal dyspepsia, sometimes associated with an irritation of the surface epithelium and periodically bringing about a transitory inflammation of the mucous membrane. These are the same conditions as found in other non-anemic cases of gastric achylia; they offer the real features of what are called gastrogenous dyspepsia. As in all these forms their appearance changes, now present for a shorter or a longer time, now ceasing suddenly and permitting stools of completely normal character or a state of mild constipation. Therefore it may happen they are only identified by carefully inquiring into the previous history, as they are absent during the period of observation. In the majority of my cases transitory diarrhea and gastric achylia, which was present in all my cases except one, preceded the development of the anemia many years.

There is marked harmony between my observations and those of Faber, especially as to the pre-anemic digestive troubles. Endeavoring to answer the question in which way achylia may lead to anemia, Faber believed it to be by way of the intestine. According to his suggestion the lack of hydrochloric acid gives rise to the establishment of hemolytic bacteria in the small intestine, but he did not prove either the existence or the nature of the supposed intestinal disorders. This was omitted by all the earlier authors, as, for instance, Martius, who sought the cause of pernicious anemia in atrophy of the mucous membrane, proceeding from the stomach to the duodenum and small intestine. As to my experience, not only is the frequency of intestinal dyspepsia in pernicious anemia striking, but even more so in the frequent occurrence of various degrees of anemia in all forms of chronic intestinal dyspepsia. The percentage of serious forms of anemia occurring in the course of gastrogenous dyspepsia is much higher than that occurring in simple achylia not connected with diarrhea. Thus the common non-specific intestinal dyspepsia forms the missing link between achylia and pernicious anemia.

We cannot here thoroughly discuss the theories concerning the real causes of intestinal disorders following gastric achylia. Faber's suggestion, based on the passage of pathogenic bacteria through a stomach not containing hydrochloric acid, a theory established long ago by Baumann and his pupils, is indeed useful, because the condition of chronic intestinal dyspepsia cannot be understood without the coöperation of bacterial fermentation. But surely the lack of hydrochloric acid cannot by itself entirely explain the problem. The connective tissue and other food remains which are not dissolved in the achylic stomach contents may be accused with more probability, as they are not only a lurking place, but also a good culture medium for decomposing bacteria, which under these conditions settle in the duodenum. Together with burdening of the intestine with insufficiently dissolved food, they slowly lead to a state of exhausted pancreatic digestion, which can sometimes be proved by the appearance of unchanged nuclei in the feces.

Turning now to the anatomical lesions, the glossitic changes known as Hunter's tongue can be observed in the majority of cases. Microscopic investigation shows proliferation of the epithelial covering alternating with atrophic spots, fissures, mild degrees of lymphocytic exudation, and other signs of chronic inflammation. Streptococcic invasion, found by Hunter, can only be regarded as accidental. It may also be noticed that irritability of the tongue, corresponding to the characteristic appearance, sometimes precedes the anemia (Matthes).

Faber and Bloch, who studied the microscopic structure of the stomach in achylia, found the lymphatic follicles enlarged and indistinctly shaped, lymphocytes more or less spread through the mucous membrane, and the glands diminished in number and size, doubtless signs of chronic inflammation, but no atrophy.

As to the intestine, the question introduced by Nothnagel as to whether an atrophic state of larger parts of the mucous membrane, like those occasionally seen in the stomach, are in any way to be found, can be answered in the negative. Though the macroscopic features of a thin, pale, and transparent intestinal wall, especially met with in cases of pernicious anemia, seems to disprove that careful microscopic examination of the whole intestine, prepared immediately after death, shows only the same pathological changes as in the stomach. Even by comparing the weight of the whole mucous membrane with that of a normal one, and by counting the number of Lieberkühn's glands in sections from different parts, Meyer and v. Lippmann in my laboratory, agreeing with Faber and Bloch, found no atrophy. There were the same signs of a slight chronic inflammation of the mucous membrane as found in the stomach.. Only once did I observe a fresh inflammation in the lower part of the ileum.

Gathering up these facts, we must conclude that the anatomical lesions corresponding to the functional disorders do not show any specific character, that they must be regarded rather as the result than as the cause of the digestive disturbances. Hunter's suggestion of a primary infectious origin of pernicious anemia is proved neither by anatomical nor by bacteriological facts.

But the fact of coincidence of the gastro-intestinal lesions with the anemic condition cannot prove their causal connection. Are there any arguments to make evident the hemolytic nature of these lesions? Though it is well known, and can easily be demonstrated, that the blood taken from the peripheral veins in pernicious anemia does not show or seldom shows signs of hemolysis, such as colored serum or decreased resistance of the red corpuscles to salt-solution, there are some remarkable facts supporting the theory of a hemolytic agent especially circulating in the portal venous system. The first, produced by Hunter himself, is the excessive accumulation of iron in the liver, which is more than three times as great as under normal conditions, and does not bear a correct relation to the amount of iron in the spleen and the kidneys. The other fact, exhibited by M. B. Schmidt and communicated by Matthes, is the reddish (hemolytic) color presented only by the portal lymph vessels and lymph nodes in patients who died from pernicious anemia.

Accepting the suggestion of a hemolytic agent entering into the portal system, the question arises whether it is produced in the chyme or in the mucous membrane of the bowels. The presence of an increased amount of hemolytic substances in the intestinal contents or in the feces, if ever proved—as it has not been—cannot satisfy us, because the decomposition of almost all sorts of food sets free transitory traces of oleic acid. This acid is shown by Tallquist and Faust to be an efficient hemolytic substance; the normal epithelium must be able either to withstand such a noxious substance or, if absorbed, to destroy its toxic character by changing its structure. By the same reason the researches of Lüdke and Fejes, who extracted hemolytic substances out of the different intestinal bacteria, especially from the Bacillus coli, isolated from pernicious anemia, do not explain anything, as so far there is no evidence that the bacteria penetrate the covering epithelium and grow within the mucous membrane.

On the other hand, Korschun and Morgenroth produced hemolytic lipoids from different normal organs; for instance, from the mucous membrane of the intestine, the pancreas, etc. Starting from that fact, Berger and Tsuchiya in two of our cases of pernicious anemia immediately after death prepared the mucous membrane of the whole gastro-intestinal tube. The lipoids extracted from the stomach, and even more from the small intestine, showed a hemolytic power about ten times higher than those of normal organs. I believe this result to be of great importance, although Ewald and Friedländer could not confirm it. But they omitted to examine fresh organs.

Remembering the microscopic signs of chronic inflammation, mentioned before, we are justified in supposing certain degenerative changes in the mucous membrane of the small intestine which may set free hemolytic substances. It is obvious that the constant absorption of even a small quantity by an organ, especially destined for absorption, can exhaust the reproductive power of the bone marrow.

Another fact, just stated by Kabanow in my laboratory, may confirm this suggestion. Working with the new Abderhalden method of proving the origin of diseases by searching for the so-called specific protective ferments circulating in the blood, Kabanow in three cases of pernicious anemia found the mucous membrane of the small intestine regularly, that of the stomach only once, but that of the colon, liver, etc., never decomposed by the serum. This means that the small intestine and in a lesser degree also the stomach, undergoes degeneration.

If the experiences hitherto spoken of seem to confirm the causal connection between certain digestive disturbances and the development of pernicious anemia, I do not believe that all cases of this disease have this origin. Only one-third of the patients suffering from pernicious anemia show marked intestinal troubles, and the number of dyspeptic persons who acquire severe anemia is not higher. Moreover, experience shows that the anemic condition when once developed, does not always go parallel with the intestinal troubles. While the latter improve and relapse, the anemia often maintains its progressive character even when the digestion has improved under careful treatment. Schaumann studied the fate of his patients who recovered from bothriocephalus anemia and found that part of them still inclined to relapsing anemia. This observation and other circumstances induced him to believe that a constitutional state forms the basis upon which different lesions may give rise to pernicious anemia. Indeed, Bartlett, Pateck, Matthes, and others, saw striking examples of family or hereditary development of the disease. Pernicious anemia can be produced also by causes which have no connection with the gastro-intestinal tube, such as lues, pregnancy, septic infection, chronic nephritis, etc., though the intestine as the chief place of absorption prevails. If the experiment newly made by Eppinger and Delcastello, that extirpation of the spleen is able to cure certain cases of pernicious anemia, should be confirmed in the future, we must deal with the possibility of an accumulation of the hemolytic agent in the spleen, as Banti supposes to take place in the disease called after him.

The blood changes of pernicious anemia, interpreted by the hematologists as a degeneration of blood formation, leads to the same suggestion of a various etiology of the disease. There is no proof that only toxic irritation of the bone marrow produces the megaloblastic type of blood formation. Every sort of exhaustion can do the same. Often the first attack can be combated by stimulating the blood-forming organs with arsenic. If the cause of permanent blood dissolution is at once removed the anemia may disappear.

It is useless to discuss a problem which cannot be solved with our present knowledge. Turning to the more practical question, Do the facts in any way influence our treatment of pernicious anemia? Grawitz, who first accepted Hunter's theory, based his opinion more on his successes in treating the anemic with a carefully composed diet and with systematic washing of the stomach and colon than on pathological investigations. We all know the difficulties of feeding these patients. The irritability of the tongue and stomach is extreme, and makes them refuse all except soft food. Regarding the constant lack of hydrochloric acid in the stomach and the intestinal dyspepsia depending on it, we can give some rules which must be observed in the diet. The first is to banish all irritating substances, such as salt, spices, too hot or too cold food, sparkling drinks, high percentage alcoholics, etc. All food must be minutely chopped or mashed because the stomach, which by its juice should assimilate the injested material, does not functionate as it should. By the same reason all raw food, as fruits, salads, raw or smoked meat, etc., are not permitted. Whatever is eaten must be thoroughly cooked or grilled.

As to the combination of the food, I do not agree with Grawitz, who, fearing that the decomposition of albuminous material could supply the hemolytic agent, put his patients on a vegetarian regime. Personally, I do not prefer any particular food, but adapt the diet in each case to the report of the feces examination, which must be repeated at least every other day. If the stool shows fermentation of carbohydrates (acid reaction, remains of starch and iodophilous bacteria, production of gas in the thermostat), all vegetables, potatoes, rice, bread, sometimes even sweets, must be avoided for some days. Later, under control of the feces they may be allowed. On the other hand, evident putrefaction of the stool (with alkaline reaction, increased fragments of muscle fibers, etc.) affords restriction of the albuminous food (meat, eggs, etc.), and a more farinaceous or milk diet. Changing the regime has of itself a good effect.

As achylia of the stomach is a constant symptom of pernicious anemia, it is usual to give the patients hydrochloric acid with the meals. I sometimes exclude arsenic and other drugs, but am convinced that by regular use of hydrochloric acid not only the intestinal disorders will be diminished, but also the anemic state can be considerably improved. Grawitz, Cottan, and others have reported cases treated and cured by hydrochloric acid alone. If hydrochloric acid proves uselss, I recommend systematic washing of the stomach with physiological salt solution or salicylic acid solution (1 to 1000). More efficient are insufflations of oxygen directly into the intestine by the duodenal tube. Grawitz applied lavage of the colon with 2 per cent. salt solution, and emphasized their effect. My own experience is too slight to form an opinion about them, but I believe it is better to wash the duodenum than the colon. I prefer these methods to the use of disinfecting drugs as none of them has proved satisfactory.

As mentioned previously, the improvement of anemia does not always keep pace with the disappearance of the intestinal disorders, yet subsequent care for the latter has a real effect also on the former. Preceding the development of anemia, the digestive troubles should be noticed as early as possible and submitted to careful treatment. Prophylaxis is always safer than healing the fully developed disease. Here, as in other branches of internal medicine, our motto must be: *Principis obsta.*

THE RELATION OF GLYCOSURIA TO PITUITARY DISEASE AND THE REPORT OF A CASE, WITH STATISTICS.*

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The extraordinary influence of the pituitary gland upon the metabolism and development of the body is now universally conceded. Cushing[1] has grouped the disturbances of the hypophysis cerebri under the term "dyspituitarism," the manifestations being due partly to primary involvement of the gland and partly to the effects of pressure upon neighboring structures.[2] That pituitary disease, however, occasions secondary alterations in the functions of certain internal secretions is quite probable. In support of the fact that hyperthyroidism may be consequential to lesions of the hypophysis, we desire to report a case of acromegaly with glycosuria in which there were manifestations of exophthalmic goitre.

The patient, A. H., aged forty-six years, occupation cook, weight 170 pounds, and height 5 feet 9½ inches, first fell under the care of my surgical colleague, Dr. William L. Rodman, in the Medico-Chirurgical Hospital, at which time she was suffering from a gangrenous wound, inflicted by a fish bone, of the left hand. On December 12, 1913 (a few days later), the patient was referred to the medical service—to us—for study and treatment. It should be stated at the outset that the left hand continued to show swelling, was very painful, and presented a large gangrenous ulcer on the

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